Origin and Description of Pueraria mirifica

Premarket Notification for

Pueraria candollei var. mirifica root extract

as a New Dietary Ingredient

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I. Introduction

Pueraria candollei var. mirifica Airy Shaw & Suvatabandhu (hereinafter referred to as *P. mirifica*) is a Thai plant noted for very large bulbous rhizomes that grow along its roots. The dried powder of the root has traditionally been used as a folk remedy for menopause-related vasomotor symptoms for centuries. The root of *P. mirifica* has been sold as a food supplement or non-prescription herbal medicine to the general public in Thailand for over fifty years.

Characterization studies carried out since the mid-twentieth century have determined that the rhizomes of *P. mirifica* contain various phenolic compounds, many of which are found in common food products such as the soybean. In recent years, the properties of the dried powder obtained from this root have been studied further. Efforts at assaying the root by HPLC (High Performance Liquid Chromatography) fingerprint analysis have been ongoing for several years. The marker compounds identified in P. mirifica root include: daidzin, puerarin, genistein, genistin, and daidzein.

This document is submitted in support of a notification of intent to market an extract of the dried powder of the root of *Pueraria candollei* var. *mirifica* Airy Shaw et Suvat (*P. mirifica*) as a new dietary ingredient. This extract is chemically similar in composition to the crude root, as will be documented in this submission, based on recent independent analytical work completed in the United States. **The safety of the Pueraria mirifica extract that is the New Dietary Ingredient referred to in the enclosed Notification to FDA dated December 17, 2003 is thus supported by the historical use of *Pueraria mirifica* root, as well as studies on the root extract.**

II. Origin and Description of *P. mirifica*

P. mirifica is a member of the family Leguminosaea, sub-family Papilionoideae, belonging to the soybean and pea sub-family of plants. In general, the *Pueraria* species are strong climbers, creeping in and over low vegetation or climbing up tall trees. At least 76 different sub-species of *Pueraria* have been taxonomically identified world-wide, many of which are found in Asia, Australia, Africa and North, Central and South America.[1] *P. mirifica* is found within the boundaries of Thailand, primarily in mixed forest areas located in the north, west, and northeast parts of the country, at elevations between 300 and 800 meters.[2, 3]

P. mirifica is a perennial woody climber, with multiple large tubers along its root system that can weight 10 to 70 kilos per tuber. A voucher sample of *P.*

mirifica is kept at the School of Agriculture, University of Chiang Rai, Thailand. A taxonomist's certified voucher sample of the plant parts of *P. mirifica* is on file at Flora Research Laboratory, Inc., Grants Pass, Oregon, dated February 12, 2002, and certified by Thawatchai Wongprasert, Taxonomist, Thai Herbarium Center, Department of Forestry, Ministry of Agriculture.[4] *P. mirifica* is also cultivated for study purposes in experimental plots at various Thai agricultural universities.

III. History and Traditional Use of *Pueraria candollei var. mirifica*

According to historians, the root of *Pueraria mirifica* was first described over 900 years ago in Buddhist scriptures discovered in the ruins of the ancient city of Pookham City (Pukam; now located in Burma [Myanmar]).[5] Traditionally, *Pueraria mirifica* root has been used by Thai women in and around Thailand for the relief of vasomotor symptoms (hot flashes and night sweats) associated with menopause.[5] As part of the current practice of botanical medicine in Thailand, menopausal women are encouraged to consume the roots of *Pueraria mirifica* in powder form orally once a day before bedtime to alleviate hot flashes and night sweating.[5]

IV. Chemistry of *P. mirifica* Root Extract

Extracts of *P. mirifica* root have been characterized extensively and contain three main classes of compounds: phytosterols, isoflavonoids (isoflavones and isoflavone glycosides), and coumestans.[6-17] A number of individual constituents have been identified in *P.mirifica* root:

a. Phytosterols:

beta-sitosterol
deoxymiroestrol
isomiroestrol
isomiroestrol-7-methyl ester
miroestrol
miroestrol-3-methyl-ester

b. Isoflavonoids:

i. Isoflavones

daidzein (7,4'-dihydroxyisoflavone)
genistein (5,7,4'-trihydroxyisoflavone)

kwakhurin (3-[2-(3,3-dimethylallyl)-4,6-dihydroxy-3-methoxyphenyl]-7-hydroxyisoflavone)
kwakhurin hydrate
formononetin (7-hyrdroxy-4′-methoxyisoflavone)

ii. Isoflavone glycosides

daidzin (daidzein-7-O-glucoside)
genistin (genistein-7-O-glucoside)
puerarin (6′- *O*-beta-apiofuranoside)
puerarin-6″-monoacetate
mirificin (puerarin-6″-*O*-beta-apiofuranoside)

c. Coumestans

coumestrol (3,9-dihydroxycoumestan)
mirificoumestan (3,9-dihydroxy-8-methoxy-7-(3,3-dimethylallyl)-coumestan)
mirificoumestan glycol (3,9-dihydroxy-8-methoxy-7-(2,3-dihydroxy-3-methylbutyl)-coumestan)
mirificoumestan hydrate

d. Others

(+)-tuberosin
pterocarpene
puemiricarpene (3,9-dihydroxy-8-methoxy-7-prenylpterocarpene)

It has been claimed that the HPLC peak characterized as miroestrol may actually represent the presence of deoxymiroestrol in the extract.[18] This finding suggests that this peak (and therefore the miroestrol content of the sample of extract being analyzed) may be artifactual, resulting from a combination of deoxymiroestrol and isomiroestrol that occurs during the sample isolation procedure. This may explain why independent confirmation of miroestrol has not been reported.

HPLC analysis of *P. mirifica* is charactrerized by two tall peaks on the HPLC, shown as peak 1 and peak 2, which represent miroestrol and puerarin, respectively, while the smaller peaks 3 through 5 represent daidzin, genistin, and daidzein, respectively.[19]

V. Extraction Process and Quality Control of *P. mirifica* Root Extract

Recent unpublished studies carried out in Thailand have identified what factors determine quality control important to *P. mirifica* wildcrafting, including: species identification, location, atmospheric conditions during growth, age of plant at harvest, harvesting period, drying methods, storage conditions, and production processes. The following conclusions have been drawn concerning the variability of the composition of *P. mirifica* root:[20]

- *P. mirifica* obtained from the same sub-species and location (province, district, village or mountain) and during the same harvesting period have the same fingerprint, but exhibit different peaks on HPLC analysis. This suggests that they contain the same chemical constituents but may vary somewhat quantitatively.
- *P. mirifica* obtained from the same sub-species and location but during different harvesting periods exhibit increased variability in the quantities of the phenolic compounds that they contain. The differences can be as great as three-fold.
- *P. mirifica* obtained from the same sub-species and during the same harvesting period but from different locations are slightly different in both HPLC fingerprint and peak heights. This suggests that there are small differences in chemical composition and that the quantities of phenolic compounds present may vary to some degree.
- *P. mirifica* of the same sub-species but harvested from different locations and during different harvesting periods may have up to a 10-fold difference in the quantity of phenolic compounds present.

Because the phenolic content of *P. mirifica* can vary, extraction methods began in the 1980's to produce a product that would most closely resemble the phenolic content found in nature according to traditional practices for selection, harvesting, drying, storage, and production.

Moreover, laboratory standards are available for the isoflavone glycosides puerarin, daidzin, and genistin and the isoflavone, daidzein, that can be used as marker compounds during standardization. Miroestrol cannot be used for quantitative standardization of *P.mirifica* because no laboratory standard exists.

Companies offering *P. mirifica* extracts in Thailand have developed quality control/quality assurance (QC/QA) procedures compliant with good manufacturing practices for harvesting, storage, and manufacture. These procedures and practices were developed under guidance from the Thai Ministry of Public Health and the Thai Food and Drug Administration (TFDA) and National Institutes for Health (TNIH) of the Thai Ministry of Agriculture, with assistance from the Department of Pharmaceutical Chemistry, Mahidol University, Thailand.[21] In addition, the harvesters of *P. mirifica* in Thailand

are required to receive extensive training and must be approved as wild-crafters by the Forestry Department of the Thai Ministry of Agriculture.

Chemical Equivalence of P.mirifica extract to crude P.mirifica root powder

In order to determine if their *P. mirifica* root extract is similar in composition to the crude root, Smith Naturals commissioned quantitative analyses of lots of crude samples and had them compared to the extract by High Performance Liquid Chromatography (HPLC) at the laboratory facilities of Flora Research (San Juan Capistrano, CA USA), an independent analytical laboratory. (On September 28, 2003, Flora Research relocated to Grants Pass, OR USA.)

Sample preparation for the crude and the extract of *P. mirifica* is slightly different. This required method development by the lab as part of its quality assurance. Beginning in late 2002 and ending in early January, 2003, Jim Kababick, who is also the Chair of the AOAC Methods Committee for Dietary Supplements, and the Director of Flora Research, and Mark Roby, (PhDs in organic and physical chemistry), Flora Research's Laboratory Director, completed a full validation package for the analysis of both the extract and the crude of *P. mirifica*. Method development included standards for purity and UV spectra, instrument detection limits, instrument quantification limits, linearity, and accuracy/precision.[22]

A voucher sample of *Pueraria candollei var. mirifica* was also sent to Flora Research.[23] The electronic scanning photo taken of the label of the voucher sample sent to Flora Research shows that it was collected by Mr. Th. Wongprasert and colleagues, all certified wildcrafters, certified by the Ministry of Agriculture, Department of Forestry, Thailand and is attached.[24]

In early May, 2003, Flora Research received six (6) lots marked "Pueraria mirifica" from Smith Naturals that were coded as follows:

CPM – KK / SA – 35
DPM – SA – 29
DPM – SA – 35
CPM – LB – 42
CPM – KC – 35
DPM – LB – 42

Flora Research performed quantitative analysis of puerarin, daidzin, daidzein, genistin and genistein of each lot by high performance liquid chromatography (HPLC). Analytical work was completed on May 9, 2003. Prior to completion of

the report of the results, Smith Naturals disclosed to Flora Research that the lots were coded as follows:

DPM lots = crude extract
CPM lots = crude powder

On June 10, 2003, Flora Research released a signed summary of the results for each lot analyzed, titled "Analytical Report."[25]

HLPC results were reported for puerarin, daidzin, genistin, and daidzein. (Genistein could not be quantified due to an unknown interfering compound as noted in the laboratory report.)

Table 1.

Results of Quantitative Analysis of Puerarin, Daidzin, Genistin, Daidzein in milligrams per gram (mg/g):

	Puerarin	Daidzin	Genistin		Daidzein
Crude Samples (n=3)	0.433	0.122	0.037	0.070	
	0.343	0.071	0.029	0.035	
	0.311	0.069	0.027	0.035	
Ave.	**0.362**	**0.087**	**0.031**		**0.046**
Extract Samples (n=3)	0.310	0.108	0.025	0.061	
	0.351	0.077	0.024	0.040	
	0.263	0.068	0.024	0.030	
Ave.	**0.308**	**0.084**	**0.024**		**0.044**

Table 2 shows the average scores for the six lots based on the Analytical Report for the crude versus the extract sample lots with the difference between the averages shown in milligrams per gram (mg/g):

Table 2.

Marker Compound	Ave. Crude (n=3) (mg/g)	Ave. Extract (n=3) (mg/g)	Difference

Puerarin	0.362	0.308	0.054
Daidzin	0.087	0.084	0.003
Genistin	0.031	0.024	0.007
Daidzein	0.046	0.044	0.002

The results reported in the June 10, 2003, Analytical Report (Exhibit D) show non-significant differences for the four compounds analyzedbetween the crude powder and extract samples.

The above data confirm that Smith Naturals' *P. mirifica* root extract is chemically similar to crude *P. mirifica* root powder. The company's extraction process does not concentrate constituent levels beyond the variable levels naturally found in the plant.

VI. Estrogenic and Estrogen Antagonistic Phytoestrogen Isoflavones of *P. mirifica* Root Extract

Structural similarities between miroestrol and estradiol suggested that miroestrol-containing *P. mirifica* might possess estrogenic properties. Subsequently, it was reported that *P. mirifica* exhibited weak estrogenic activity, comparable to that exhibited by some soy products, when fed to ovariectomized rats.[26,27]

P. mirifica contains inactive glucosides of the plant phytoestrogen isoflavones, genistein and daidzein. Ingestion of glucosides derived from phytoestrogens is followed by complex enzymatic conversions in the human gastrointestinal tract that produce the biologically active heterocyclic phenols, genistein and daidzein.[28] These phenols exhibit weak estrogenic activity when present in low concentrations (less than 1% of the estrogenic activity of an equimolar concentration of estradiol[29]). For example, the ingestion of foods containing substantial amounts of the phytoestrogen glucosides has significantly reduced the incidence of hot flashes in perimenopausal women.[28,30]

In contrast, these compounds act as estrogen antagonists when they are present in higher concentrations.[31,32] It is likely that the estrogen antagonist activity of plant phytoestrogen isoflavones is not mediated by the estrogen

receptor and therefore is capable of inhibiting the expression of the weak estrogenic effects of low concentrations of these compounds.[28]

VII. Safety of *P. mirifica*

All studies discussed henceforth used extracts of *P. mirifica* provided by Smith Naturals. All crude samples of *P. mirifica* were either supplied by Smith Naturals or by the Thai Ministry of Health, Department of Medical Sciences. The same certified wildcrafters, certified by the Department of Agriculture, Department of Forestry, who supply Smith Naturals with the crude for their extract product supply the Thai Ministry of Health with crude product.

Bacterial Mutagenicity (AMES) Assay

P. mirifica root extract is not mutagenic and is without toxic effect in laboratory animals during long-term ingestion of up to 6 times the recommended daily human dose. Acute exposure to the equivalent of 14,000 human doses, evaluated over 14 days, or to the equivalent of 45,000 human doses, consumed over 90 days, have produced no evidence of toxicity. Daily intake of 6 times the recommended daily human dose has not produced adverse effects or signs of toxicity in healthy menstruating women aged 20 to 49 years during 6 months of continuous daily supplementation. Testimonial letters from experts have attested to the safety of *P. mirifica* extract in humans. *P. mirifica* root extract is safe for human use as traditionally recommended for up to 6 months of continuous use.[33]

P. mirifica root extract is not mutagenic. Two Ames tests of *P. mirifica* (Smith Naturals, Bangkok) were conducted in June of 2001, using the incubation method where the results were the mean standard deviation of two plates from two independent experiments. The mutagenicity assay was performed according to standard methodology.[34,35] Control solvents included distilled water and dimethyl sulfoxide (DMSO). Salmonella typhimunum strains TA 98 and TA 100 were obtained from Dr. Taijiro Matsushima (Japan Bioassay Research Center, Japan Industrial Safety and Health Association, Kanagawa, Japan). Two-fold criteria were used for data evaluation. The tested materials were to be considered to be mutagenic when a dose-related increase in relevant colony count was observed, the number of colonies per plate with the test substance is more than twice that of the negative control, and when a reproducibility of test results is observed. *P. mirifica* extract test results were consistently negative.[36,37]

Animal Studies

Several animal toxicology studies have been completed on *P. mirifica* using both crude powders and Smith Natural's extract.

P. mirifica extract produced no toxic effects or changes in liver function or gross pathology when given to rats in daily doses of 2000 mg/kg of body weight for up to 14 days.[38.39,40] This level of intake (2000 mg/kg for 14 days) is equivalent to a total exposure of up to 28,000 mg/kg and is comparable to 1,000 recommended daily doses (2 mg/kg) taken daily or 14,000 recommended daily doses total consumed over 14 days in humans.

In an attempt to determine the LD_{50} for *P. mirifica* extract, a single *P. mirifica* crude powder dose of 40 g/kg (equivalent to 20,000 the recommended daily doses taken at one time) was administered orally yet failed to induce signs of toxicity in mice.[41]

In long-term feeding experiments, daily doses of 10 mg/kg of body weight (equivalent to 5 times the recommended daily dose) or 100 mg/kg of body weight (50 times the recommended daily dose) failed to produce toxic effects when given to mice for 90 days (total cumulative exposure: 270 mg or 2700 mg, respectively).[41] In the same study, a daily dose of 1000 mg/kg of body weight of *P. mirifica* extract given orally for 90 days (equivalent to about 45,000 recommended daily doses) induced reversible anemia and pathologic changes in the kidneys and testicles.[41]

More detailed descriptions of the studies cited follows hereafter.

a. Acute Toxicology Studies

P. mirifica extract was given to mice (ICR species; 10 males and 10 females) by gavage in two doses of 20 g/kg of body weight, 6 hours apart. The mice were then observed for 14 days. No mortality, signs or symptoms of toxicity, or gross pathological changes were found.[42] *P. mirifica* extract tested was Lot No. DPM-SA-29C/29E (Smith Naturals Co Ltd., Bangkok) confirmed by a certificate of analysis for the lot by HPLC, conducted on June 12, 2001, by the Department of Chemistry, Rangsit University, Bangkok. (Marker compounds were identified as 1 through 5 with an index provided to each compound to the right of the chromatogram.)[43]

The previous study was repeated three times, with identical results, by the Department of Medical Sciences, Ministry of Public Health, Bangkok, on May 24, 2001 (Lot No. SPM (DPM)-SA-25-PE); July 12, 2001 (Lot No. SPM (DPM)-

SA-29C); and July 12, 2001 (Lot No. SPM (DPM)-SA-29E). At the end of each study, the Ministry's toxicologists stated:

> "Observation results show that *Pueraria mirifica* powder given as 40 g/kg produced no signs or symptoms of acute toxicity in mice and did not cause animal deaths. Therefore, the LD-50 value is greater than 40g/kg."[42]

An acute toxicity study was performed in male and female rats using *P. mirifica* extract (Lot # L020943/SMP-SA-05, Smith Naturals, Co., Ltd., Bangkok) given orally. A confirmatory HPLC fingerprint was done by the Department of Chemistry, Rangsit University, Bangkok, Thailand (Lot# L020943/SMP-SA-05 chromatogram.)[44] The dose of extract given was based on a recommended daily dose of 100 mg of *P. mirifica* extract for a woman weighing 50 kg. Male and female rats were given daily doses of *P. mirifica* extract containing 0.126 or 0.63 micrograms of miroestrol (10 and 50 times the recommended daily dose, respectively) via intragrastric tube. No significant evidence of toxicity was found in either sex at the lower dose (0.126 micrograms). However, at the higher dose (0.63 micrograms), significantly higher organ weights and increased blood chemistries were noted, but these were not considered to be of a pathological significance or nature.[40]

b. Subacute and Subchronic Toxicology Studies

Liver enzymes and function were studied in 20 male albino rats given either 0, 10, 100 or 200 mg/kg of body weight of *P. mirifica* extract for 14 days via intragastric tube. On day 15, blood was collected via the infraorbital sinus and the serum examined for GOT and GPT activity. A histopathologic examination of the liver was performed. No significant histopathological differences were found between the treated and control groups; however, the size of liver cells in the *P. mirifica*-treated rats at the dosage of 10 mg/kg was found to be smaller than in the rats given placebo. This finding was not found in the liver tissues of rats receiving the two higher doses.[39]

In an oral subacute toxicology study, young adult Sprague-Dawley rats were given *P. mirifica* extract at a dose of 2,000 mg/kg of body weight for 14 days. At the end of the study, no mortality, signs or symptoms of toxicity, or gross pathological changes were found.[38]

c. Chronic Toxicology Studies

A chronic toxicology study in rats treated orally with *P. mirifica* extract at daily doses of 10, 100 and 1,000 mg/kg of body weight for 90 consecutive days revealed that the growth rate and food consumption of rats receiving *P. mirifica* extract at the daily doses of 100 and 1,000 mg/kg were significantly lower than those of the control groups. Hematological results indicated that *P. mirifica* extract at the daily dose of 1,000 mg/kg caused anemia with significant decreases in hematocrit, the number of erythrocytes, and plasma hemoglobin, in both sexes. Two weeks after withdrawal of supplementation with *P. mirifica* extract, the hematologic changes in male rats reversed, whereas in only two out of four females, the hematocrit returned to normal. The numbers of white blood cells and platelets in male rats receiving the highest dose were significantly lower than those of the control group but these changes were not observed in female rats of the same dose group. Serum biochemical examination showed that total cholesterol concentrations in male rats receiving *P. mirifica* extract at each dose were significantly lower than that of the control group; these changes were observed in females only at the daily doses of 100 and 1,000 mg/kg. At post-mortem examination, the weights of both testes from male rats receiving the highest dose were significantly lower than those of the control group. The uterus of females receiving 100 and 1,000 mg/kg appeared swollen and the actual uterine weights and percent relative uterine weights of these two groups were significantly higher than those of the control group. Histopathological examinations indicated that male rats receiving the highest daily dose of *P. mirifica* extract had a significantly higher incidence of testicular hyperemia than the control group. Female rats receiving the highest daily dose of *P. mirifica* extract had significantly higher incidence of kidney tubular casts than did the control group. Taken together, it was concluded by the investigators that *Pueraria mirifica* at the daily doses of 10 and 100 mg/kg given orally in rats did not cause any significant pathologic changes.[41]

Human studies

A safety and efficacy study was conducted at a university hospital in Japan by a Japanese and Thai university research team studying the safety of crude *P. mirifica* root powder in healthy menstruating women. This Japanese-Thai study was conducted at the School of Medicine, Saint Mariane University, Tokyo, Japan. Fifty healthy menstruating volunteer females, ages 20 to 49, were given between 100 to 600 mg orally of *Pueraria mirifica* root powder (Smith Naturals, Bangkok) daily in capsules for 7 days, two weeks after menstruation. The crude root powder was obtained from a certified harvester in Kanchanaburi Province, Thailand, and confirmed taxonomically and by HPLC fingerprint as *P. mirifica* root. Compared to pre-study measurements, there were no significant changes in female hormones (serum estrogen, urine estrogen, urine pregnanediol concentrations), kidney function (total urine

volume, specific gravity, creatinine clearance), blood chemistries (plasma total protein, triglycerides, sodium, potassium, chloride, calcium, or total phosphate concentrations; serum total cholesterol concentrations; plasma GOT or GTP activities), white blood cell counts (neutrophil [segmented and non-segmented], eosiniphil, basophil, lymphocyte, and monocyte), hematocrit, plasma hemoglobin concentrations, blood platelet counts, white blood cell counts (WBC), or red blood cell counts (RBC) 14 days after oral intake ended. Six out of 50 subjects (12%) reported that they menstruated earlier or later than expected. There were no reports of abnormally heavy, severe, or missed menstruation.

In a letter received from Dr. Smitasiri, an Associate Professor of Reproductive Physiology at the University of Mae Fah Luang, Thailand and a study participant, dated January 17, 2002,[45] he states that the data from this study "shows a very low order of side effects and no significant changes in any clinical markers during the 4 week period of this study."

Adverse Event Monitoring

An inquiry to the Thai Ministry of Public Health, which regulates food supplements, and the country's expert on *P. mirifica*, resulted in two letters[46,45] attesting to the safe record of use of this food supplement.

In Thailand, *P. mirifica* is regulated as an over-the-counter food supplement by the Thai FDA. The first letter[46] is authored by Dr. Pakdee Pothisiri, Director-General of the Department of Health, Ministry of Public Health, Thai Ministry of Public Health. He is also the former Director of the Thai FDA and Director-General of the Department of Medical Sciences. In addition, he is a former Senior Researcher at the U.S. NIH, and former Chairman of the Codex Alimentarius Commission of the World Health Organization/United Nations in Rome. Thailand's FDA is a department in the Ministry of Public Health.

The second letter is the letter is from Prof. Yuthana Smitasiri, referred to above on this page.[45] He has studied *P. mirifica* for over 20 years as an animal toxicologist and specialist in reproductive physiology at three Thai universities. The Thai Ministry of Public Health regards Prof. Smitasiri as the leading expert on *P. mirifica*. Both letters state that in Thailand there is no record of any significant adverse events reported by the Thai population relative to the use of crude *P. mirifica* root or *P. mirifica* root extract.

VIII. Summary

Given the widespread and historic use of *P. mirifica* root as a botanical medicine and food supplement for the relief of vasomotor symptoms associated with menopause, combined with the evidence from animal toxicological studies, the Japan-Thai safety/efficacy study in healthy women, and written verification of the lack of adverse reports associated with its consumption in the country of origin where it has been in wide use as a traditional botanical remedy for menopausal symptoms, in crude and extract form, the risk associated with human consumption of *P. mirifica* root extract sold as a dietary supplement is extremely low.

Supporting this opinion is another letter from Dr. Yuthana Smitasiri. In this letter, dated January 23, 2002,[47] he further states:

> "*P. mirifica* has been available as a traditional medicine in Thailand for over fifty years, and a regulated herbal medicine for the last 10 years. It is a popular herbal medicine today throughout Thailand and even neighboring countries such as Burma (Myanmar). Although health claims are not permitted for this botanical, it is offered by more than 25 different Thai manufacturers and can be found readily available in public markets, pharmacies, and health clinics. No prescription is required and it is not registered as a drug but as a food supplement. Toxicology studies in various animals have been conducted at Thai universities on several animal species and been found to be non-toxic at levels of intake well above those recommended for use by Thai manufacturers. Considerable work has been done by Thai university chemists and foreign chemists characterizing the principle compounds found in *P. mirifica*, with particular interest shown in the isoflavones, many of which are found in soybeans, which is not surprising as *P. mirifica* is a member of the same botanical family. Since the contents of *P. mirifica's* isoflavones varies depending on the time of harvest and location, there is increasing demand among health practitioners for the extract of the product to insure consistent levels of the major isoflavones found in the finished product.
>
> Manufacturers generally recommend a daily intake of between 50 to 100 milligrams of the extract or crude powder. No contraindications are known. No significant non-transient adverse events have been reported to date."

In Dr. Smitasiri's opinion, *P. mirifica* root powder probably has been used by Americans of Thai descent for many years in the United States, primarily as a benefit "for their aging parents or relatives, to continue their family's traditional use of this botanical." He also points out that, "One of the principle

reasons for Thai people consuming this root in crude or semi-crude form, or as an extract, is to relieve symptoms associated with the end of menstruation in women, which is often referred to as "post-menopausal symptoms."[47]

Finally, Health Canada has not objected to the importation of *P. mirifica* into Canada.[48]

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